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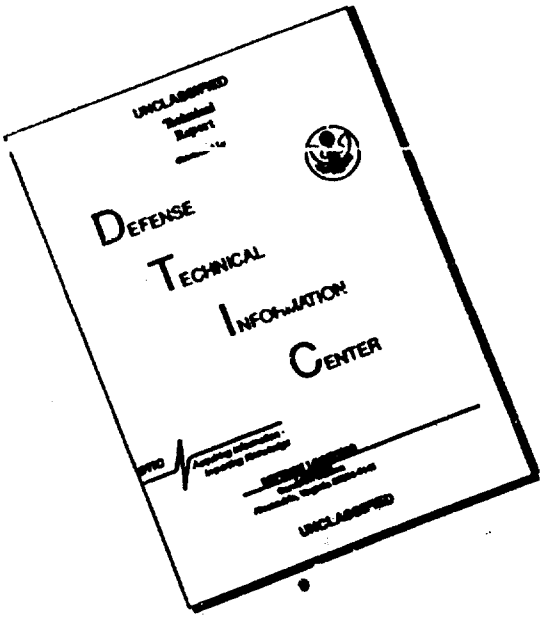

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13. ABSTRACT *(Maximum 200 words)*

This study was designed the effects of exercise performed on animals already injured with *E. coli* endotoxin. This would tell us whether exercise makes the lung injury worse. It would also tell us how much exercise performance is impaired. These studies were designed to give further insights into the underlying causes of acute lung injury. Premature termination of the study prevented completion of the research project. It appeared from the limited experimentation conducted that maximal exercise was impaired by endotoxin-induced lung injury. Conclusions regarding exacerbation of endotoxin-induced lung injury cannot be made.

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FOREWORD

The opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army

In conducting research using animals, the investigator adhered to the "Guide for the care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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INTRODUCTION

Acute lung injury is likely to occur from the consequences of the modern battlefield.

- Nitrogen dioxide (NO_2) and various acid halides (HF, HBr, HCl) can be found in extremely high concentrations when an anti-tank round penetrates an armored vehicle (1).
- Many chemical and biological agents target the pulmonary system as their route of exposure.
- Exposure to intense blast overpressure occurs behind defeated armor and around various high explosive munitions (1).

Acute lung injury from these causes is characterized by pulmonary edema, inflammation and hemorrhage. While the pathologic presentation of these injuries is similar, studies to date have shown that post-exposure exercise causes different effects (see Status below). It would be of benefit to the field commander to know, for these potential injuries, how physical activity after a lung insult will affect the severity of injury. Treadmill exercise tests in goats/sheep allow a means of evaluating the effects of exercise on the severity of lung injury.

The exacerbation of injury by exercise will yield important information on the underlying pathophysiological mechanisms of lung injury. This is particularly important because soldiers might be exposed to a variety of acute lung injury mechanisms (e.g., blast, NO_2, halides, chemical agents, toxins, etc.), which present with pulmonary edema but which respond differently with exercise. Analysis of the time course of injury exacerbation gives a better understanding of microvascular permeability increases and its underlying causes.

The most common cause of Adult Respiratory Distress Syndrome (ARDS) is gram-negative sepsis, and endotoxins are believed to be the offending agents which cause injury to various organ systems including the lungs (2). The last ten years has seen a large number of investigations of the effects of endotoxin lung injury in animals (3). Most popular has seemed to be the intravenous infusion of E. coli endotoxin into unanesthetized sheep. This animal model produces effects which are very similar to clinical ARDS, namely diffuse noncadiogenic lung edema, hypoxemia and decreased lung compliance. The investigations using this model have focused on trying to determine the underlying mechanisms of the acute lung injury. Our proposed studies will explore the relationship of endotoxin lung injury and exercise so that future studies (see Future Studies below) will investigated the mechanisms of this interaction as well as ARDS alone.

Animal models of exercise are being increasingly used where invasive measurements are needed or when the effects of exercise on abnormal states are being investigated. Sheep have proven to be a better model of maximal exercise than rats, dogs, or horses (4).

Few studies have focused on the effect that acute lung injury has on the exacerbating effects of exercise on acute lung injury. Maximal exercise performed immediately and up to 24 hr after exposure significantly worsens NO_2-induced lung injury (5). However, pulmonary contusion injury is worsened by maximal exercise performed 1 hr after exposure but not by 24 hr exercise (6). It has been proposed that exercise performed before the onset of increased microvascular permeability would not exacerbate injury while exercise performed after the onset of edema would exacerbate injury. Studies by Lehnert and Stavert (7), however, did not show this. Exercise performed during the latency period after inhalation exposure to perfluroisobutylene (PFIB) (i.e. no pulmonary edema for 8 hrs) did not exacerbate lung injury. However, exercise performed during the latency period after inhalation exposure to bis(trifluromethyl)disulfide (TFD) (i.e. no pulmonary edema for 3 hrs) did exacerbate pulmonary edema and inflammation. It is clear from these studies that the interaction of acute lung injury and exercise will differ depending on the cause of the lung injury. The etiology of this difference is unknown.

The present study proposes to study the exercise exacerbating effects using an accepted model of acute lung injury. Infusion of E. coli endotoxin into the pulmonary artery causes pulmonary hypertension and increased lung vascular permeability resulting in pulmonary edema (8-9). Infiltration of granulocytes and release of arachidonic acid metabolites into the blood and lymph are hallmarks (10-11). We propose to investigate the effects of post-exposure exercise on lung injury induced by endotoxin administration. Endotoxin injury was chosen for several reasons:

1. Endotoxin lung injury is a well accepted model of acute lung injury with numerous publications using the model. However, the effects of exercise and endotoxin injury have not been described. We hope to put together what is known about this lung injury model with exercise data from this study to gain further insight into the interaction of lung injury and exercise.

2. Endotoxin lung injury can be induced safely in a laboratory without expensive or complicated facilities.

3. The results would be directly applicable to the soldier in the field who might be exposed to a variety of biological warfare weapons which use biological toxins.

Endotoxin lung injury differs from other lung injury models which have been used with exercise. Endotoxin lung injury is induced by systemic endotoxemia as opposed to the inhalation route of administration used with the other models. As a result, endotoxin lung injury has little or no latency period before the presentation of overt lung injury (i.e. edema, inflammation). In addition, pulmonary hypertension is a characteristic of endotoxin lung injury which is not been reported in the other lung

injury models. The extent to which these differences affect the interaction of lung injury and exercise is unclear.

BODY

METHODS

a. Surgery: All animals were surgically prepared with a chronic carotid loop to facilitate collection of arterial blood. Surgeries were performed in the surgical Suite, Bldg 40. Animals were allowed to recover at least 3 weeks before treadmill training was begun.

b. Treadmill Training: Sheep/goats were exercised with the use of a treadmill fitted with a cage surrounding the treadmill belt. Speed and grade (elevation, angle of inclination) were independently varied. The animals' heads were minimally restrained with a set of vertical padded bars placed behind the caudal aspect of the mandibles. A canine anesthesia mask modified with a 3 cm i.d. connector was held on the animal with a muzzle. A 2-way non-rebreathing valve for direction of inspired and expired air was attached to the muzzle. Expired air was conducted by 4 cm i.d. corrugated tubing a exercise data acquisition system (Horizon, Sensormetik). Oxygen consumption ($\dot{V}o_2$) was calculated from $\dot{V}_E$ and F_Eo_2.

All animals were kept closely sheared in order to avoid overheating during exercise. Hooves were kept trim. Sheep/goats were run at 1.5 mph for 2 min and then 3 mph for 8 min at 0% grade every day for 2 weeks. During the 3rd and 4th weeks, animals were run at 1.5 mph for 2 min, 3 mph for 2 min and 4 mph for 10 min three times per week (preferably with a day of rest between challenges).

c. Data Collection: Prior to data collection (i.e. not during treadmill training), the sheep/goats were fasted for 24 hr but were allowed free access to water. Cardiopulmonary parameters as well as arterial and venous blood gases and CO-oximetry and peripheral white blood cell count were collected at the specified time periods and used to monitor the severity of lung injury. After topical anesthesia, animals were intubated nasotracheally using a fiberoptic bronchoscope and prepared with an arterial catheter and a venous thermodilution catheter as well as an esophageal balloon. Measurements of lung resistance, dynamic compliance, FRC, cardiac output, mean arterial and pulmonary arterial pressures, shunt fraction, systemic vascular pressure and pulmonary vascular pressure were made. Duplicate 1 ml blood samples were collected in heparinized syringes for blood gas and CO-oximetry. Five (5) ml of venous blood were collected for white blood cell count determination.

Prior to exercise challenge, the animal were extubated and the esophageal balloon removed. Indwelling arterial and thermodilution catheters remained for the exercise challenge. Arterial and pulmonary arterial pressures were monitored continuously during exercise. Arterial and venous blood were collected every 1.5 min during exercise for determination blood gases and CO-oximetry.

At the completion of the studies animals were euthanitized with an overdose of I.V. Pentobarbital. The sheep were placed in dorsal recumbency and the carotid arteries severed to allow for rapid exsanguination. The lungs, trachea, and heart will be removed *in toto*. The heart were cut away, any frank blood or fluid were drained and the lungs weighed.

RESULTS

Results of the 2 goats performed on this protocol are included in Appendix A and B.

CONCLUSIONS

No definitive conclusions can be made from these data since insufficient data was collected. It seems clear that if more animals had been performed, endotoxin would have been shown to decrease exercise capacity. A significant decrease in $\dot{V}o_2$ was observed in both animals.

Several agents have been used to investigate the mechanisms of endotoxin lung injury. Studies to date seem to show that LPS-induced pulmonary hypertension and increased lung permeability are the result of different mechanisms. Thromboxane inhibitors attenuate pulmonary hypertension but not lung permeability changes (12-13). In addition, neutrophil depletion reduces increased pulmonary vascular permeability without affecting pulmonary hypertension (14). Other agents have been shown to attenuate both hypertension and edema including prostaglandin E_2 (15), calcium channel inhibitors (16), and steroids (17-18). On the other hand, diethylcarbamazine, a lipoxygenase inhibitor, did not affect the pulmonary vascular response to endotoxin (19). This protocol proposed to characterize the interaction of endotoxin lung injury and exercise. Future studies in this area should investigate the effect of some of these inhibitors, particularly those that modulate vascular permeability, on endotoxin lung injury after exercise.

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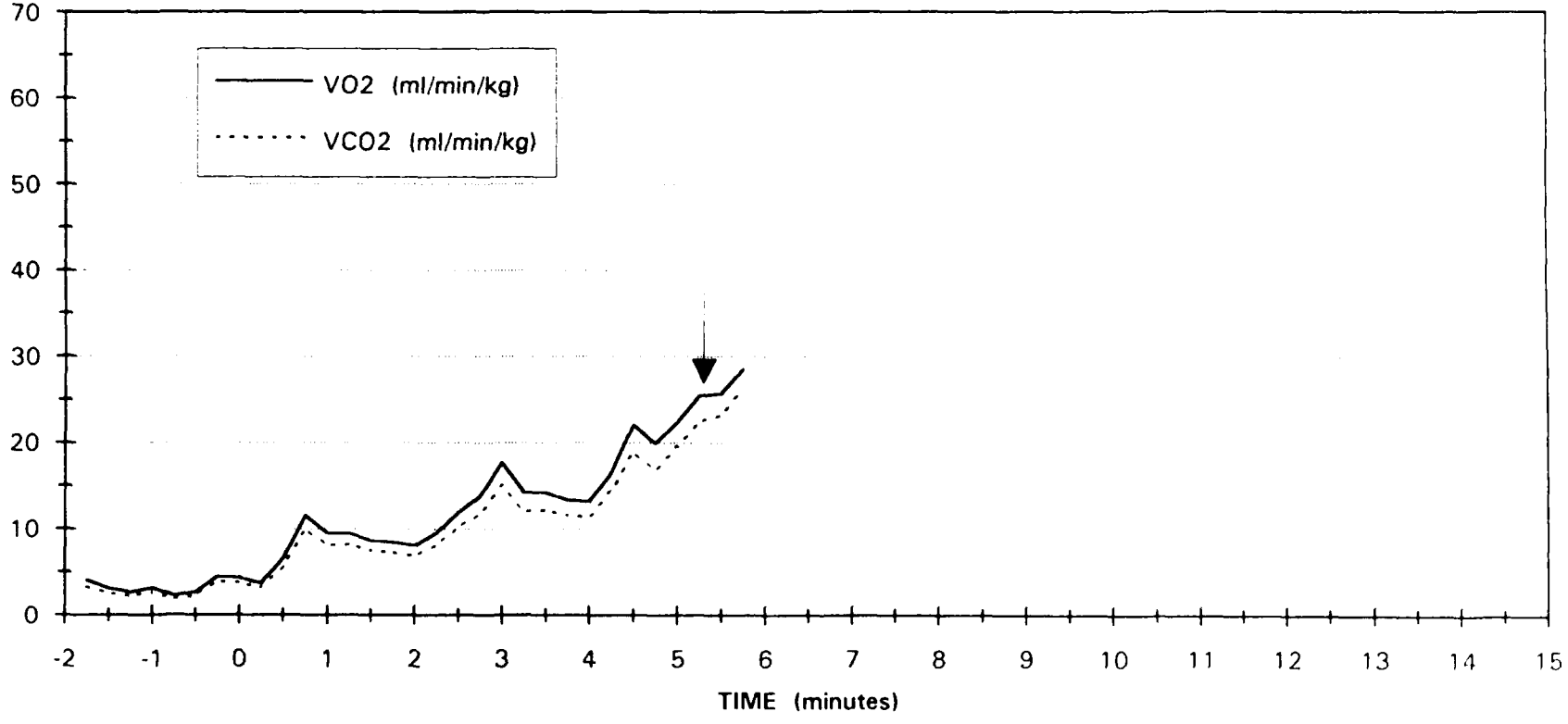
APPENDIX A

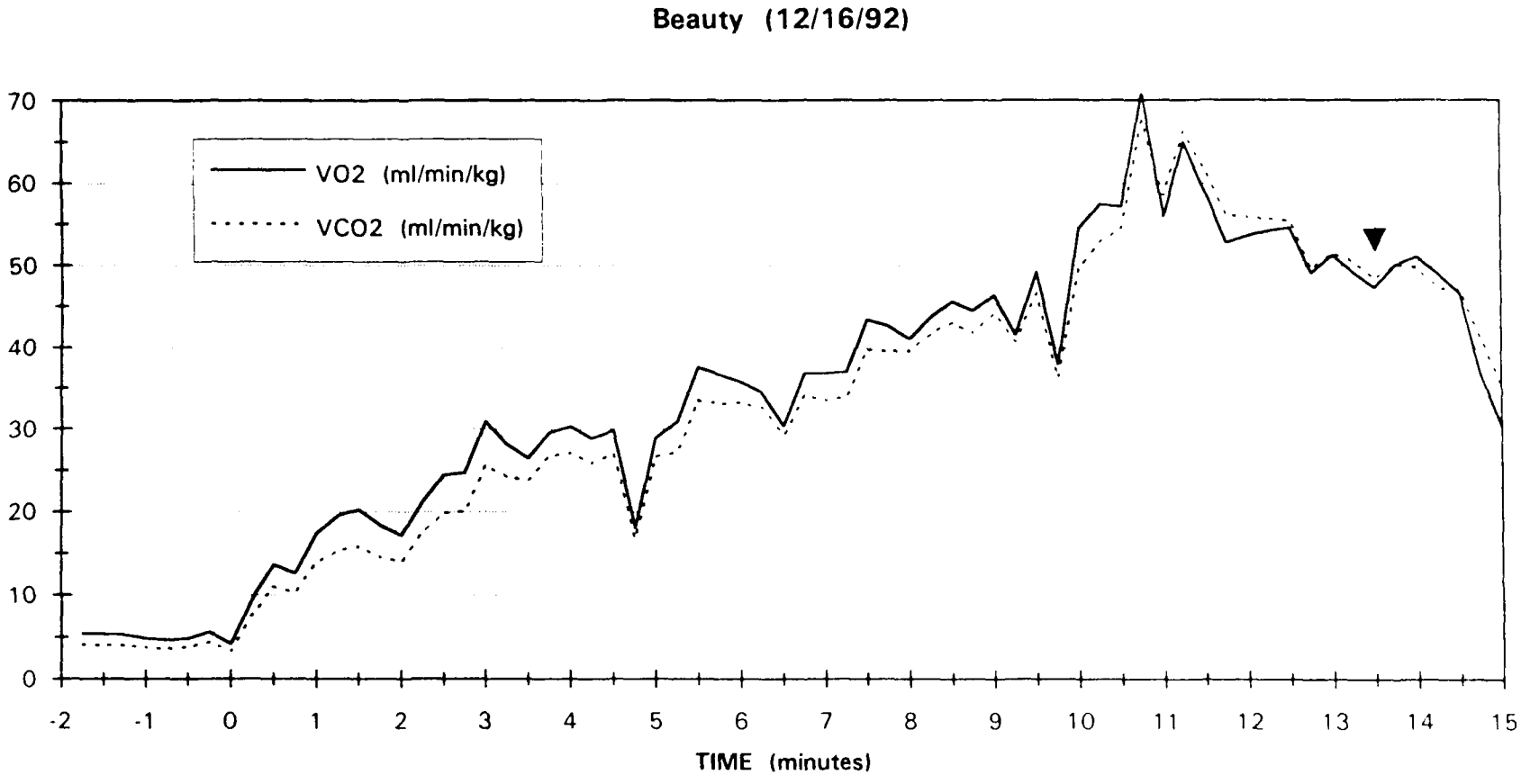
SUMRYBEU XLS

ANIMAL	Beauty								
DATE:	Dec 16 17, 1992								
WT:	Day 1 = 37 lb; Day 2 = 35 lb								
Lung Wt:	200.3 gm								
	Control Rest	Control Post Ex	Pre Endo	Imm Post Endo	30 min Post Endo	60 min Post Endo	Post Exercise	90 min Post Endo	120 min Post Endo
BLOOD GAS									
Arterial									
pH	7.395	7.421	7.366	7.352	7.336	7.324	7.304	7.311	7.329
pCO2	32.2	29.0	37.0	28.5	35.5	38.2	36.6	36.1	40.3
pO2	128.4	117.1	128.9	107.4	125.6	110.1	114.4	124.3	111.3
HCO3	18.8	18.0	20.2	15.1	18.0	18.9	17.3	17.3	20.2
TCO2	19.7	18.8	21.2	15.8	19.0	19.9	18.3	18.3	21.3
BE	-3.5	3.4	-3.2	-7.5	5.7	-5.3	7.1	6.9	4.2
Venous									
pH	clotted	no sample	7.348	7.308	7.303	7.297	7.205	7.259	7.292
pCO2			41.7	47.1	42.8	45.7	57.5	46.7	44.1
pO2			63.3	45.0	54.9	47.9	46.2	57.0	65.2
HCO3			21.8	22.4	20.1	21.2	21.5	19.8	20.3
TCO2			23.0	23.7	21.3	22.5	23.1	21.1	21.5
BE			-2.1	-2.2	-4.4	-3.5	-5.6	5.9	-4.8
CO-OXIMETRY									
Arterial									
tHb	10.5	13.4	10.1	10.2	15.9	14.7	13.8	13.6	14.7
HbO2	96.1	95.7	95.9	94.8	95.5	94.9	95.3	95.5	94.6
HbCO	1.3	1.6	1.2	1.2	1.4	1.3	1.3	1.3	1.4
MetHb	0.9	0.8	1.0	0.9	0.8	0.8	0.8	0.8	0.8
O2ct	14.0	17.8	13.5	13.4	21.1	19.4	18.3	18.1	19.3
SAT	98.3	98.1	98.1	96.8	97.6	96.9	97.3	97.5	96.7
RHb	1.7	1.9	1.9	3.1	2.3	3.0	2.6	2.4	3.2
O2cap	14.3	18.2	13.7	13.9	21.6	20.0	18.8	18.5	20.0
Venous									
tHb	clotted	no sample	10.4	12.0	15.7	14.1	14.2	14.5	14.5
HbO2			79.5	43.0	66.9	51.8	41.5	68.0	77.7
HbCO			1.2	0.7	0.8	0.7	0.5	0.9	1.0
MetHb			0.8	0.8	0.9	0.9	1.0	0.9	0.9
O2ct			11.3	7.2	14.6	10.2	8.2	13.7	15.7
SAT			80.1	43.7	68.1	52.6	42.1	69.2	79.2
RHb			19.5	55.5	31.4	46.6	57.0	30.2	20.4
O2cap			14.2	16.4	21.5	19.3	19.4	19.8	19.8
WBC 10(9)/L			16.7	5.4	5.9	4.7		4.5	4.0
VE	4.239	48.760	3.194	4.410	3.301	2.624	16.305	2.545	3.279
FiO2	.2092	.2092	.2085	.2086	.2081	.2073	.2073	.2089	.2089
FiCO2	.0008	.0008	.0008	.0009	.0013	.0011	.0011	.0011	.0008
FeO2	.1891	.1847	.1868	.1927	.1844	.1872	.1795	.1877	.1876
FeCO2	.0164	.0241	.0186	.0140	.0188	.0182	.0267	.0207	.0196
VO2/kg	5.043	71.031	4.358	4.415	4.930	3.315	28.492	3.383	4.415
VCO2/kg	3.897	67.552	3.570	3.637	3.635	2.829	26.237	3.134	3.884
HR			101	93	108	113	174	124	122
MAP			111	118	92	73	103	113	91
PAP			8	30	17	17	22	18	20
PAWP			1	11		2		2	7
CVP			0		2			6	10

ANIMAL	Beauty									
DATE	12/16/92	(Control Exercise)								
	Rest	1.5 min	3.0 min	4.5 min	6.0 min	7.5 min	9.0 min	10.5 min	12.0 min	13.5 min
BLOOD GAS										
Arterial										
pH	7.395	7.408	7.403	7.411	7.399	7.400	7.409	7.361	7.409	7.421
pCO2	32.2	32.4	32.7	32.2	34.4	30.7	31.6	37.4	32.7	29.0
pO2	128.4	139.2	120.2	123.2	126.8	135.3	120.2	101.6	117.8	117.1
HCO3	18.8	19.5	19.4	19.5	20.3	18.1	19.0	20.1	19.7	18.0
TCO2	19.7	20.4	20.3	20.4	21.2	19.0	19.9	21.2	20.6	18.8
BE	3.5	-2.6	2.8	-2.5	2.2	-3.9	2.9	3.3	-2.4	-3.4
Venous										
pH	clotted	clotted	7.345	7.360	7.355	7.343	7.345	7.309	no sample	no sample
pCO2			47.3	45.0	43.7	40.3	43.9	49.2		
pO2			51.1	50.7	52.5	52.1	47.8	50.4		
HCO3			24.6	24.2	23.3	20.8	22.8	23.5		
TCO2			25.9	25.5	24.5	22.0	24.0	24.8		
BE			0.1	0.2	0.6	-2.8	-1.1	-1.6		
CO-OXIMETRY										
Arterial										
tHb	10.5	11.7	11.9	12.2	13.1	11.5	13.3	13.6	14.5	13.4
HbO2	96.1	96.2	96.1	96.1	96.1	96.3	95.1	93.9	95.4	95.7
HbCO	1.3	1.4	1.3	1.6	1.6	1.5	1.6	1.4	1.6	1.6
MetHb	0.9	0.9	1.0	0.7	0.6	0.9	0.7	0.7	0.7	0.8
O2ct	14.0	15.6	15.9	16.3	17.5	15.4	17.6	17.8	19.2	17.8
SAT	98.3	98.5	98.4	98.4	98.3	98.7	97.3	95.9	97.6	98.1
RHb	1.7	1.5	1.6	1.6	1.7	1.3	2.6	4.0	2.3	1.9
O2cap	14.3	15.9	16.2	16.6	17.8	15.6	18.1	18.5	19.7	18.2
Venous										
tHb	clotted	clotted	13.5	13.2	13.7	11.8	14.2	14.8	no sample	no sample
HbO2			61.8	62.0	63.7	62.9	55.0	58.5		
HbCO			1.0	1.0	1.1	1.0	1.0	0.9		
MetHb			0.7	0.8	0.7	0.7	0.7	0.7		
O2ct			11.6	11.4	12.1	10.3	10.9	12.0		
SAT			62.9	63.1	64.9	64.0	56.0	59.5		
RHb			36.5	36.2	34.5	35.4	43.3	39.9		
O2cap			18.4	18.0	18.7	16.1	19.4	20.2		

Beauty (12/17/92)



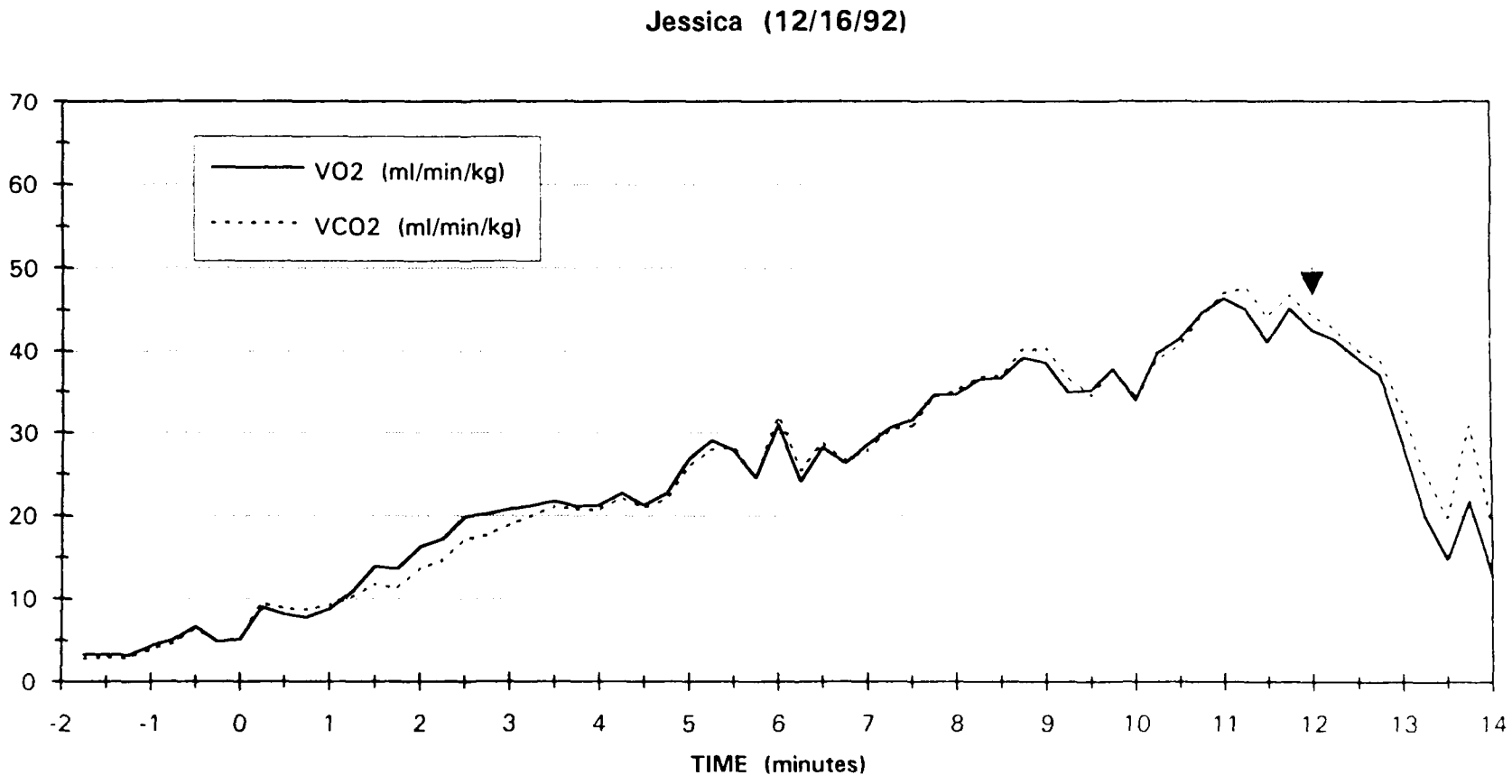

Beauty (12/16/92)
VO2 (ml/min/kg)
VCO2 (ml/min/kg)
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
TIME (minutes)

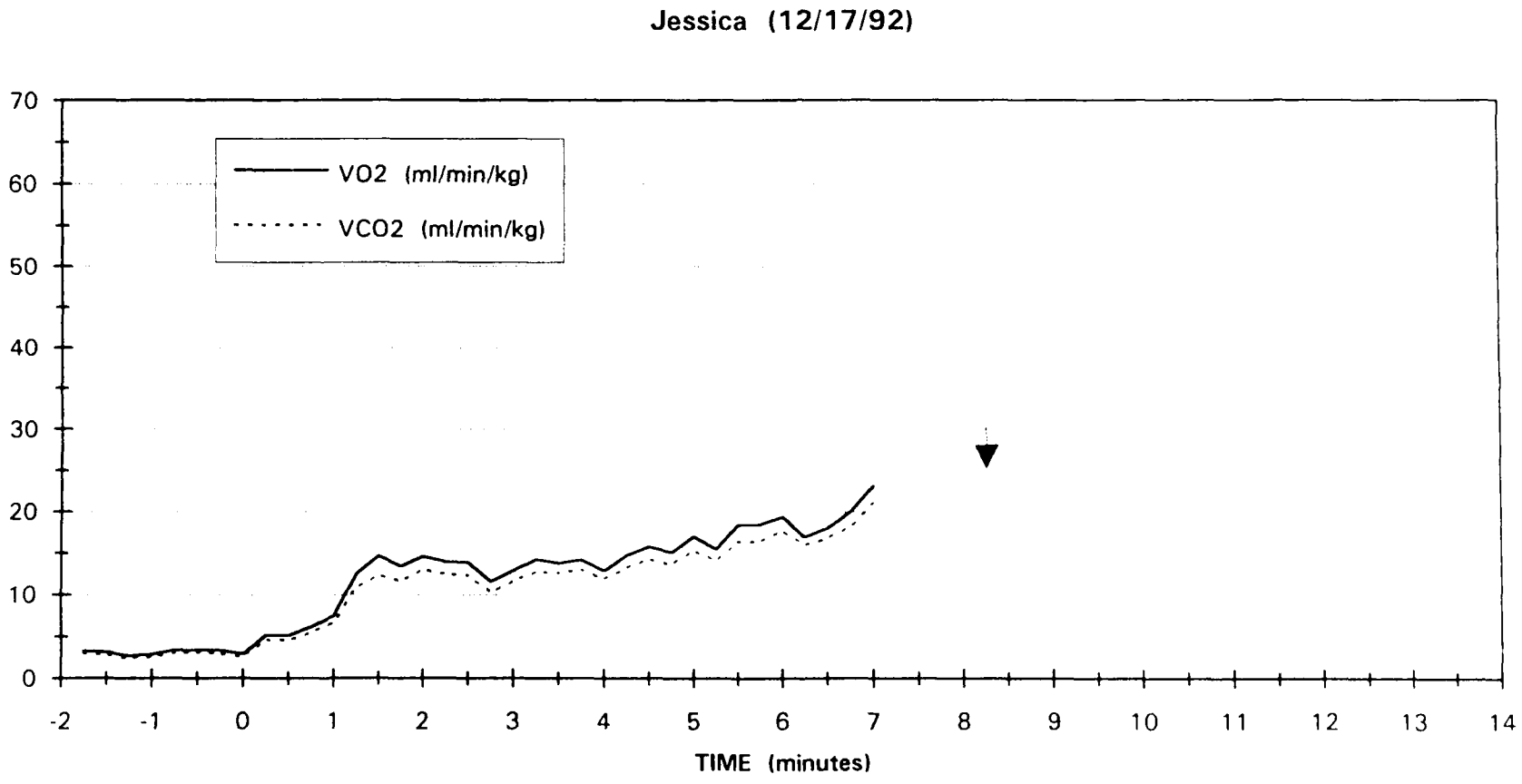
APPENDIX B

ANIMAL:	Jessica								
DATE:	Dec 16 17, 1992								
WT:	Day 1 = 70lb; Day 2 = 73 lb								
Lung Wt:	483.0 gm								
	Control Rest	Control Post Ex	Pre Endo	Imm Post Endo	30 min Post Endo	60 min Post Endo	Post Exercise	90 min Post Endo	120 min Post Endo
BLOOD GAS									
Arterial									
pH	7.367	7.393	7.394	7.389	7.392	7.382	7.380	7.398	7.395
pCO2	31.6	28.0	36.6	35.0	34.0	35.3	32.9	34.1	34.3
pO2	119.8	127.2	166.9	95.0	110.5	117.7	115.4	110.7	99.0
HCO3	17.2	16.3	21.3	20.1	19.7	20.0	18.5	20.0	20.0
TCO2	18.1	17.0	22.3	21.1	20.6	21.0	19.5	21.0	20.9
BE	5.5	5.5	-1.6	2.6	-2.8	2.9	4.1	-2.4	2.5
Venous									
pH	7.369	7.350	7.374	7.374	7.362	7.349	7.297	7.352	7.360
pCO2	38.3	31.4	41.4	41.7	39.7	41.2	50.1	38.3	39.7
pO2	62.4	50.4	59.3	44.9	52.5	51.8	43.5	54.5	56.3
HCO3	21.1	16.5	23.0	23.2	21.4	21.6	23.2	20.2	21.3
TCO2	22.1	17.4	24.2	24.3	22.5	22.8	24.6	21.3	22.4
BE	-2.1	-5.9	-0.4	0.0	-1.8	-2.0	-1.8	-3.1	-2.1
CO-OXIMETRY									
Arterial									
tHb	9.2	11.8	10.3	12.2	14.7	14.7	14.5	14.6	14.3
HbO2	96.8	96.2	97.0	94.4	95.9	95.2	95.2	95.4	94.6
HbCO	0.4	0.5	0.2	0.6	0.5	0.5	0.5	0.6	0.6
MetHb	1.1	1.0	1.1	0.7	0.9	0.9	0.8	0.8	0.8
O2ct	12.4	15.8	13.9	16.0	19.6	19.5	19.2	19.4	18.8
SAT	98.3	97.7	98.3	95.6	97.3	96.6	96.5	96.8	95.9
RHb	1.7	2.3	1.7	4.3	2.7	3.4	3.5	3.2	4.0
O2cap	12.6	16.2	14.1	16.7	20.1	20.4	19.9	20.0	19.6
Venous									
tHb	10.4	11.3	10.5	12.5	14.3	14.6	14.2	14.6	14.2
HbO2	81.2	67.8	77.3	52.4	68.0	69.5	46.5	72.5	74.8
HbCO	0.3	0.2	0.2	0.1	0.2	0.2	0.0	0.3	0.3
MetHb	1.0	1.0	0.7	0.8	0.7	0.9	1.0	1.0	1.0
O2ct	11.7	10.6	11.3	9.1	13.5	14.1	9.2	14.7	14.8
SAT	82.3	68.6	78.0	52.9	68.5	70.3	47.0	73.5	75.8
RHb	17.5	31.0	21.8	46.7	31.1	29.4	52.5	26.2	23.9
O2cap	14.3	15.5	14.5	17.2	19.7	20.1	19.5	20.0	19.5
WBC 10(9)/L			7.0	2.3	2.6	2.3		1.4	1.3
VE	5.977	65.228	1.770	4.122	6.080	4.963		5.427	4.470
FiO2	.2084	.2084	.2090	.2089	.2081	.2083		.2081	.2081
FiCO2	.0012	.0012	.0008	.0008	.0010	.0012		.0013	.0011
FeO2	.1838	.1848	.1829	.1871	.1939	.1884		.1876	.1837
FeCO2	.0242	.0251	.0232	.0183	.0131	.0192		.0190	.0230
VO2/kg	4.462	46.392	1.451	2.834	2.786	3.101		3.499	3.428
VCO2/kg	4.200	46.982	1.245	2.269	2.372	2.805		3.028	3.086
HR			78	79	105	102	175	116	125
MAP			106	144	117	104	109	102	117
PAP			13	37	34	28	33	26	29
PAWP			4	12	9	6		8	3
CVP			10	16	6	8	15	4	7

ANIMAL: Jessica
DATE: 12/16/92 (Control Exercise)

	Rest	1.5 min	3.0 min	4.5 min	6.0 min	7.5 min	9.0 min	10.5 min	12.0 min	13.5 min
BLOOD GAS										
Arterial										
pH	7.367	7.388	7.391	7.402	7.413	7.396	7.400	7.389	7.393	
pCO2	31.6	25.5	30.9	27.6	18.9	27.3	26.8	26.4	28.0	
pO2	119.8	122.1	122.1	125.7	136.7	126.1	156.1	133.4	127.2	
HCO3	17.2	14.6	17.9	16.4	11.5	16.0	15.8	15.2	16.3	
TCO2	18.1	15.3	18.7	17.2	12.0	16.7	16.6	15.9	17.0	
BE	-5.5	6.9	-4.3	-5.2	-8.7	-5.7	5.7	-6.5	5.5	
Venous										
pH	7.369	7.370	7.358	7.367	7.373	7.376	7.374	7.357	7.350	
pCO2	38.3	32.1	38.0	37.7	35.8	37.8	36.2	38.8	31.4	
pO2	62.4	58.6	62.3	62.2	59.9	61.7	53.7	54.9	50.4	
HCO3	21.1	17.7	20.3	20.6	19.8	21.1	20.1	20.7	[illegible]	
TCO2	22.1	18.6	21.4	21.7	20.8	22.2	21.1	21.8	17.4	
BE	-2.1	-4.7	-3.0	-2.5	-3.0	-1.9	-2.6	-2.6	-5.9	
CO-OXIMETRY										
Arterial										
tHb	9.2	8.3	9.9	9.3	6.6	10.1	11.2	10.8	11.8	
HbO2	96.8	96.9	97.0	97.9	97.1	96.2	96.8	96.4	96.2	
HbCO	0.4	0.5	0.3	-0.1	0.1	0.5	0.4	0.4	0.5	
MetHb	1.1	0.9	1.1	0.8	1.2	1.0	1.1	1.0	1.0	
O2ct	12.4	11.2	13.3	12.7	8.9	13.5	15.1	14.5	15.8	
SAT	98.3	98.3	98.4	98.6	98.4	97.7	98.3	97.8	97.7	
RHb	1.7	1.7	1.6	1.4	1.6	2.3	1.7	2.2	2.3	
O2cap	12.6	11.4	13.6	12.8	9.1	13.8	15.3	14.8	16.2	
Venous										
tHb	10.4	9.7	11.3	11.8	11.4	clotted	12.0	12.8	11.3	
HbO2	81.2	77.0	81.1	79.3	77.9		71.8	74.0	67.8	
HbCO	0.3	0.3	0.4	0.3	0.3		0.2	0.3	0.2	
MetHb	1.0	0.9	0.9	0.9	0.8		0.9	0.9	1.0	
O2ct	11.7	10.4	12.7	13.0	12.3		12.0	13.2	10.6	
SAT	82.3	78.4	82.2	80.3	78.8		72.6	74.9	68.6	
RHb	17.5	21.3	17.6	19.5	21.0		27.1	24.8	31.0	
O2cap	14.3	13.3	15.5	16.2	15.7		16.5	17.6	15.5	


Jessica (12/16/92)
VO2 (ml/min/kg)
VCO2 (ml/min/kg)
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TIME (minutes)


Jessica (12/17/92)
VO2 (ml/min/kg)
VCO2 (ml/min/kg)
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TIME (minutes)